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Atopic dermatitis: New insights and opportunities for therapeutic intervention

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Atopic dermatitis (AD) is a chronic inflammatory skin disease that frequently predates the development of allergic rhinitis or asthma. It is an important skin condition with significant costs and morbidity to patients and their families; the disease affects more than 10% of children. Recent studies have demonstrated the complex interrelationship of genetic, environmental, skin barrier, pharmacologic, psychologic, and immunologic factors that contribute to the development and severity of AD. The current review will examine the cellular and molecular mechanisms that contribute to AD as well as the immunologic triggers involved in its pathogenesis. These insights provide new opportunities for therapeutic intervention in this common skin condition. (*J Allergy Clin Immunol* 2000;105:860-76.)

Key words: Atopic dermatitis, keratinocytes, T cells, hypersensitivity, skin, allergy, superantigens, IgE

Atopic dermatitis (AD) is a chronic, relapsing, highly pruritic, inflammatory skin disease that frequently predates the development of allergic rhinitis or asthma.¹ It is an important skin condition with significant costs and morbidity to the patient, their families, and society overall. Quality of life can be severely impaired because of disruption of school, family, and social interactions as well as sleep deprivation from the intense pruritus, which is exacerbated at night. Population studies suggest that the prevalence of AD has been steadily increasing since World War II, and in most countries it now affects more than 10% of children at some point during childhood.² Interestingly, there are wide variations in prevalence both within and between countries inhabited by similar ethnic groups, suggesting that environmental factors are critical in determining disease expression.

The term "atopic dermatitis" was first introduced in the 1930s in recognition of the close association between AD

Abbreviations used

AD:	Atopic dermatitis
APC:	Antigen-presenting cell
CLA:	Cutaneous lymphocyte antigen
CTACK:	Cutaneous T-cell attracting chemokine
DBPCFC:	Double-blind placebo-controlled food challenge
FP:	Fluticasone propionate
ICAM-1:	Intercellular adhesion molecule-1
IVIG:	Intravenous γ -globulin
LC:	Langerhans cell
MCP:	Monocyte chemotactic protein
mRNA:	Messenger RNA
PDE:	Phosphodiesterase
SE:	Staphylococcal enterotoxins
TCR:	T-cell receptor
T _H 1:	T helper type 1 cell
T _H 2:	T helper type 2 cell
TSST-1:	Toxic shock syndrome toxin-1

and respiratory allergy, as well as accumulating data that exposure to allergen plays an important role in its exacerbation. However, there remains considerable debate over whether allergens really have a critical role in AD. This is more than academic because it dictates whether the clinician should look for potential allergens in the AD patient's environment and recommend allergen avoidance, just as is done as part of the management of asthma and allergic rhinitis. Indeed, recent studies suggest that the immune mechanisms underlying asthma and AD have greater similarities than differences.³ The current review will examine the cellular and immunologic mechanisms that are thought to play an important role in the pathogenesis of chronic AD (Fig 1). An understanding of the immunologic basis of AD has important implications in our approach to its management and the development of new therapies for patients with this common illness.

THE CLINICAL CHALLENGE

Intense pruritus and cutaneous hyperreactivity are major clinical features of AD.⁴ The etiology of pruritus in AD is not well understood, but it is thought to be driven by the local release of proinflammatory mediators and cytokines. Studies with intradermal injection of histamine

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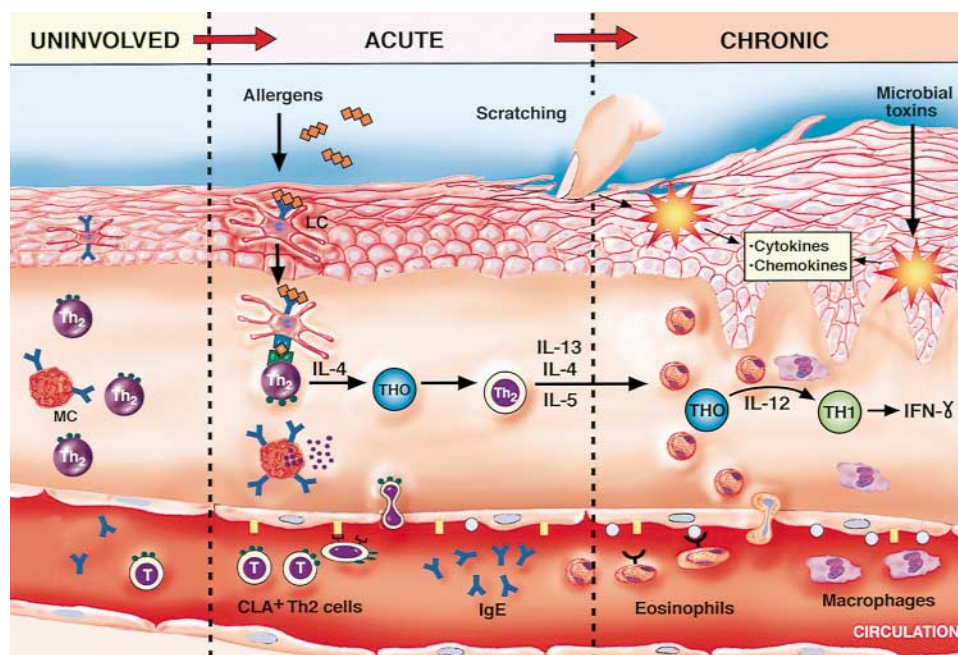


FIG 1 Immunologic pathways involved in the progression of AD. These patients have a systemic T helper type 2 (T_H2) response with elevated IgE and eosinophilia with low-level T_H2 cytokine expression in uninvolved skin. The acute skin lesions are associated with marked infiltration of T_H2 cells. However, with the infiltration of eosinophils and macrophages in chronic AD, there is a rise in IL-12 expression and a switch to T helper type 1 (T_H1) cellular responses. This biphasic switch T_H2/T_H1 switch in immune responses is paralleled clinically and histologically by acute papulation and spongiosis followed by development of lichenification, epidermal hyperplasia, and dermal fibrosis. LC, Langerhans cells; MC, mast cells; CLA, cutaneous lymphoid antigen.

as an experimental model demonstrated atopic skin to have a lower itch threshold than nonatopic skin.⁵ Furthermore, histamine levels are increased in both involved and uninvolved skin of AD. There are also more mast cells in the lichenified plaques than in uninvolved skin.⁶ Increased releasability of histamine from blood basophils of patients with AD has also been found.⁷ However, Rukwied and Heyer⁸ showed that the injection of acetylcholine intracutaneously in the skin of patients with AD treated with a potent H_1 antagonist induced significantly greater pruritus than in nonatopic controls. This suggests that pruritus in AD patients is not totally dependent on histamine release. Indeed, pruritus has also been shown to be induced by intracutaneous injection of cytokines, leukotrienes, neuropeptides, or proteases.⁹⁻¹² The potential importance of cytokines in the pathogenesis of pruritus is supported by observations that cyclosporine alleviates itching in patients with AD and that intradermal injection of IL-2 can cause intense pruritus.^{11,13} Substance P, a neuropeptide that induces mast cell degranulation, has also been found to be increased in AD skin.¹⁴

Patients with AD have a reduced threshold for irritants. With 48-hour Finn chamber testing with graded dilutions of sodium lauryl sulfate, Nassif et al¹⁵ reported that patients with active or inactive AD had significantly greater irritant skin responses than healthy nonatopic control subjects did. Although the mechanism for increased irritancy is unknown, the authors postulated that an abnormal intrinsic hyperreactivity in inflammatory cells con-

tributes to this abnormality in AD. Patients with AD frequently have dry skin and are subject to increased psychologic stress, which may lead to increased scratching, skin barrier breakdown, and development of rash.^{16,17}

The acute lesions of AD present as pruritic, erythematous, excoriated papules with extensive serous exudate superimposed on a background of erythema.¹ Repeated excoriations and trauma lead to the chronic lesions of AD, which are characterized by thickened plaques with increased markings (lichenification) and dry, fibrotic papules. In patients aged 2 years or older, AD lesions are most commonly localized to the antecubital and popliteal flexural areas. On the other hand, infantile AD generally involves the scalp, face, cheeks, and extensor surfaces of the extremities. Approximately 90% of patients have AD during the first 5 years of life. Thus patients with adult-onset AD should raise a higher index of suspicion for other diseases.

IMMUNOLOGIC FINDINGS

A systemic T_H2 response

Most patients with AD have elevated numbers of circulating eosinophils and increased serum IgE levels (Table I). Nearly 80% of children with AD eventually have allergic rhinitis or asthma, suggesting that respiratory allergy and AD have a common systemic link. Children with AD frequently have more severe asthma than do asthmatic children without AD.¹⁸ Because total serum

TABLE I. Systemic findings in AD

Increased serum IgE levels
Eosinophilia
Increased basophil spontaneous histamine release
Decreased CD8 suppressor/cytotoxic number and function
Increased expression of CD23 on mononuclear cells
Chronic macrophage activation with increased secretion of GM-CSF, PGE ₂ , and IL-10
Expansion of IL-4- and IL-5-secreting TH2 cells
Decreased numbers of IFN- γ -secreting TH1 cells
Increased serum secretory IL-2 receptor levels
Increased serum eosinophil cationic protein, eosinophil-derived neurotoxin levels, and eosinophil major basic protein levels

IgE is strongly associated with the prevalence of asthma, it raises the interesting question of whether allergen sensitization through the skin predisposes to more severe and persistent respiratory disease as a result of its effects on the systemic allergic response. Indeed, when mice are sensitized epicutaneously with protein antigen, it induces a localized allergic dermatitis, elevated serum IgE, airway eosinophilia, and hyperresponsiveness to methacholine, suggesting that epicutaneous exposure to antigen in AD may enhance the development of allergic asthma.¹⁹ Systemic activation of T cells in AD is suggested by the observation that these patients have increased numbers of circulating activated T cells and increased serum L-selectin levels, a marker for leukocyte activation that correlates with AD disease severity.^{20,21}

The elevated IgE responses and eosinophilia observed in AD reflects an increased expression of T_H2 cytokines.²² PBMCs from patients with AD have been found to have a decreased capacity to produce IFN- γ in response to a number of allergenic and mitogenic stimuli. A significant inverse correlation between IFN- γ generation in vitro and IgE serum concentrations in vivo in AD has been reported. There have also been a number of studies demonstrating increased frequency of allergen-specific T cells producing increased IL-4, IL-5, and IL-13 but little IFN- γ in the peripheral blood of patients with AD.^{23,24} PBMCs from patients with AD produce abnormally high levels of macrophage migration inhibitory factor, which is essential for T-cell activation and is expressed primarily in activated T_H2 cells.²⁵ Peripheral blood monocytes from patients with AD also have a lower incidence of spontaneous apoptosis and are unresponsive to IL-4-induced apoptosis after stimulation. This is in marked contrast to the responses of monocytes from healthy donors. The likely cause of this inhibition of apoptosis and unresponsiveness to IL-4 is increased production of GM-CSF by circulating monocytes of AD patients.²⁶

Overall, these preceding observations are important because IL-4 and IL-13 are the only cytokines that induce germline transcription at the C ϵ exon, thereby promoting isotype switching to IgE.²⁷ Both cytokines also inhibit the production of T_H1 cytokines and up-regulate CD23 on monocytes and B cells. In fibroblasts IL-4 or IL-13 stimulates RANTES, eotaxin, and monocyte chemotactic pro-

tein (MCP)-1 expression.²⁸ This likely contributes to local eosinophil infiltration and may explain why eosinophils appear only in the dermis. Because T cells do not express IL-13 receptors, exogenous IL-13 does not promote T_H2 responses or suppress T_H1 differentiation in allergen-stimulated cultures in the same way as IL-4. IL-5 and GM-CSF promotes the differentiation, vascular endothelial adhesion, and survival of eosinophils. In contrast, IFN- γ inhibits IgE synthesis as well as the proliferation of T_H2 cells and expression of the IL-4 receptor on T cells.

TISSUE LOCALIZATION OF ALLERGIC DISEASE

Location of allergic disease is determined in part by route of allergen sensitization, tissue chemokine expression, and tissue compartmentalization of the immune response. Studies in animal models have demonstrated heterogeneity in the ability of memory T cells to migrate to different tissues.²⁹ This tissue-selective homing is regulated by interaction of differentially expressed T-cell homing receptors with vascular endothelial cell surface antigens. The cell adhesion molecule that participates in T-cell homing to the skin is termed "cutaneous lymphocyte-associated antigen" (CLA). Importantly, T cells migrating into the skin of allergen-induced reactions express significantly higher levels of CLA than do T cells isolated from the airways of asthmatic subjects.³⁰ These data suggest the propensity of patients to develop AD as opposed to asthma depends in part on differences in the skin- versus the lung-homing ability of their T cells. Patients with AD have an expanded subset of activated CLA⁺ T cells in their circulation. Santamaria Babi et al³¹ analyzed the expression of CLA on circulating T cells in patients with AD versus asthma who were sensitized with house dust mite. When CLA⁺ T cells were separated from CLA⁻ T cells, the mite-specific T-cell proliferation response in AD patients sensitized to dust mite was localized to CLA⁺ T cells. In contrast, mite-sensitive patients with asthma had a mite-dependent proliferation response in their CLA⁻ T cells consistent with our observation that airway T cells have low-level CLA expression. A further link between CLA expression and skin disease-associated T cells in AD was shown by demonstrating that freshly isolated CLA⁺ T cells in AD patients, but not healthy control subjects, expressed the HLA-DR activation antigen and spontaneous production of IL-4 but not IFN- γ . More recently Akdis et al^{32,33} also demonstrated that CLA⁺ T cells in AD expressing either CD4 or CD8 spontaneously secrete IL-5 and IL-13, functionally prolong eosinophil survival, and induce IgE synthesis. Although inflammatory cells such as eosinophils are not known to have specific tissue-homing receptors, recent studies indicate that the local tissue expression of chemokines likely plays a major role in the localization to sites of inflammation. Furthermore, the newly described cutaneous T-cell attracting chemokine (CTACK/CCL27) may be involved in the attraction of CLA⁺ T cells into the skin (see below).

IMMUNOHISTOLOGY OF THE SKIN

Clinically normal-appearing skin of AD patients contains a sparse perivascular T-cell infiltrate.^{6,34} Acute papular skin lesions are characterized by marked intercellular edema (spongiosis) of the epidermis. Dendritic antigen-presenting cells (APC) (eg, LCs, macrophages) in lesional and, to a lesser extent, in nonlesional skin of AD exhibit surface-bound IgE molecules.^{35,36} A sparse epidermal infiltrate consisting primarily of T lymphocytes is also frequently observed. In the dermis of the acute lesion, there is a marked perivenular T-cell infiltrate with occasional monocyte-macrophages. The lymphocytic infiltrate consists predominantly of activated memory T cells bearing CD3, CD4, and CD45 RO (suggesting a previous encounter with antigen). Eosinophils, basophils, and neutrophils are rarely present in acute AD. Mast cells are present in various stages of degranulation.

Chronic lichenified lesions are characterized by a hyperplastic epidermis with elongation of the rete ridges, prominent hyperkeratosis, and minimal spongiosis. There is an increased number of IgE-bearing LCs in the epidermis, and macrophages dominate the dermal mononuclear cell infiltrate. The number of mast cells are increased in number but are generally fully granulated. Increased numbers of eosinophils are observed in chronic AD skin lesions. These eosinophils undergo cytolysis with release of granule protein contents into the upper dermis of lesional skin.³⁷ Eosinophil-derived extracellular major basic protein can be detected in a fibrillar pattern associated with the distribution of elastic fibers throughout the upper dermis. Eosinophils are thought to contribute to allergic inflammation by the secretion of cytokines and mediators that augment allergic inflammation and induce tissue injury in AD through the production of reactive oxygen intermediates and release of toxic granule proteins.³⁸ Eosinophil major basic protein, eosinophil cationic protein, and eosinophil-derived neutrotoxin are elevated in AD sera and correlate with disease severity.³⁹

CYTOKINE EXPRESSION PATTERN IN AD SKIN LESIONS

Role of T_H2/T_H1 cytokines

T_H2 and T_H1 cytokines contribute to the pathogenesis of skin inflammation in AD with the relative contribution of each cytokine dependent on the duration of the skin lesion. Compared with the skin of healthy control subjects, uninvolved skin of patients with AD has an increased number of cells expressing IL-4 and IL-13 but not IL-5, IL-12, or IFN- γ , messenger RNA (mRNA).^{40,41} Acute and chronic skin lesions, compared with normal skin or uninvolved skin of patients with AD, have significantly greater numbers of cells that are positive for IL-4, IL-5, and IL-13 mRNA. However, acute AD does not contain significant numbers of IFN- γ or IL-12 mRNA-expressing cells.

Chronic AD skin lesions have significantly fewer IL-4 and IL-13 mRNA-expressing cells but increased num-

bers of IL-5, GM-CSF, IL-12, and IFN- γ mRNA-expressing cells than in acute AD. Thus acute T-cell infiltration in AD is associated with a predominance of IL-4 and IL-13 expression, whereas maintenance of chronic inflammation is associated with increased IL-5, GM-CSF, IL-12, and IFN- γ expression accompanied by the infiltration of eosinophils and macrophages. The increased expression of IL-12 in chronic AD skin lesions is of interest because that cytokine plays a key role in T_H1 cell development and its expression in eosinophils or macrophages is thought to initiate the switch to T_H1 cell development in chronic AD.⁴²

Because the activity of cytokines depends on the expression of their receptors, it is of interest that acute AD lesions contain a significantly higher number of cells expressing IL-4R- α (α -subunit of IL-4 receptor) mRNA compared with chronic AD lesions and normal and uninvolved atopic skin, whereas chronic AD lesions contained significantly more cells expressing the IL-5R- α and GM-CSFR- α (α -subunit of GM-CSF receptor) mRNA compared with acute AD lesions and normal and uninvolved atopic skin.⁴³

This biphasic pattern of T-cell activation has also been demonstrated in studies on allergen patch testing.⁴² Twenty-four hours after allergen application to the skin, increased expression of IL-4 mRNA and protein is observed, after which IL-4 expression declines to baseline levels. In contrast, IFN- γ mRNA expression is not detected in 24-hour patch-test lesions but is strongly overexpressed at the 48- to 72-hour time points. This is consistent with studies demonstrating that T-cell clones obtained from early time points of evolving allergen patch test sites secrete T_H2 cytokines, whereas the majority of allergen-specific T-cell clones derived from later patch-test sites (>48 hours) exhibit a T_H1 or T_H0 type profile. Interestingly, the increased expression of IFN- γ mRNA in atopic patch-test lesions is preceded by a peak of IL-12 expression coinciding with the infiltration of macrophages and eosinophils.

A recent study using an animal model of AD examined ovalbumin-elicited allergic skin inflammation in mice with targeted deletions of the IL-4, IL-5, and IFN- γ cytokine genes to assess the role of these cytokines.⁴⁴ Their data suggested that both the T_H2 cytokines IL-4 and IL-5 as well as the T_H1 cytokine IFN- γ play important roles in the skin inflammatory response of AD. Allergen-sensitized skin from IL-5 knockout mice had no detectable eosinophils and exhibited decreased epidermal and dermal thickening, whereas IL-4 knockout mice displayed normal thickening of the skin layers but had a drastic reduction in eosinophils. Sensitized skin from IFN- γ knockout mice was characterized by reduced dermal thickening.

Chemoattractant factors

Identification of mechanisms controlling infiltration of inflammatory cells into AD skin is an area of active investigation.²⁸ Recent studies have demonstrated that IL-16, a chemoattractant for CD4⁺ T cells, is more highly expressed in acute than in chronic AD skin lesions.⁴⁵ The

C-C chemokines, RANTES, MCP-4, and eotaxin have also been found to be increased in AD skin lesions and likely contribute to the chemotaxis of eosinophils and T_H2 lymphocytes into the skin.^{46,47} Recent studies suggest a role for CTACK/CCL27 in the preferential attraction of CLA⁺ T cells to the skin.⁴⁸ The chemokine receptor CCR3, which is found on eosinophils and T_H2 lymphocytes and can mediate the action of eotaxin, RANTES and MCP-4, has been reported to be increased in nonlesional and lesional skin of patients with AD.⁴⁷ Leukotriene B₄ is also released on exposure of AD skin to allergens and may act as a chemoattractant for the initial influx of inflammatory cells.⁴⁹

Prolongation of skin inflammation

Chronic AD is linked to the prolonged survival of eosinophils and monocyte-macrophages in atopic skin. The rise in IL-5 expression during the transition from acute to chronic AD likely plays a role in the prolongation of eosinophil survival and function. In chronic AD there is also a marked increase in GM-CSF expression.²⁶ GM-CSF plays an important role in maintaining the survival and function of monocytes, LCs, and eosinophils.²⁶ Enhanced production of GM-CSF by epidermal keratinocytes and infiltrating macrophages has been shown in AD lesions.^{26,50} Supernatants from cultured keratinocytes of AD patients induced a significantly higher proliferative response in PBMCs than did supernatants from control keratinocytes of nonatopic individuals, and this proliferative response could be totally abrogated by an anti-GM-CSF mAb. Supernatants from phorbol myristate acetate-stimulated keratinocytes from patients with AD, together with exogenous IL-4, also supported the maturation of monocytes into dendritic cells. Epidermal keratinocytes, when stimulated simultaneously with IFN- γ and TNF- α , were found to produce increased levels of RANTES, which enhanced the chemotaxis of eosinophils.^{51,52} This may serve as one mechanism by which the rise in IFN- γ during chronic AD enhances the chronicity and severity of eczema. Mechanical trauma can also induce the release of TNF- α and many other proinflammatory cytokines from epidermal keratinocytes.⁵³ Thus chronic scratching plays a role in the perpetuation and elicitation of skin inflammation in AD.

The environmental triggers that contribute to chronicity of AD are unknown. However, chronic AD is frequently associated with colonization by superantigen-producing *Staphylococcus aureus*.⁵⁴ To examine a potential role for microbial superantigens in the prolongation of monocyte-macrophage survival, Bratton et al⁵⁵ incubated peripheral blood monocytes from AD subjects with various concentrations of toxic shock syndrome toxin-1 (TSST-1), a prototypic superantigen, and examined the incidence of apoptosis. TSST-1, in a concentration-dependent manner, significantly inhibited monocyte apoptosis and stimulated production of the prosurvival cytokines GM-CSF, IL-1 β , and TNF- α . Their data further showed that GM-CSF production was the primary cytokine responsible for inhibition of apoptosis.

Finally, recent studies on mononuclear cells from patients with atopic asthma indicate that allergen-induced immune activation can alter the T-cell response to glucocorticoids by inducing cytokine-dependent abnormalities in glucocorticoid receptor binding affinity.⁵⁶ Of interest, PBMCs from patients with chronic AD also have reduced glucocorticoid receptor binding affinity, which can be sustained with the combination of IL-2 and IL-4.⁵⁷ Endogenous cortisol levels have been found to control the magnitude of cutaneous allergic inflammatory responses suggesting that impaired response to steroids could contribute to chronic AD.⁵⁸

FACTORS DRIVING T_H2 CELL DEVELOPMENT IN AD

A number of determinants support T_H2 cell development early in the atopic skin process and provide opportunities for therapeutic intervention. These include the cytokine milieu in which T-cell development is taking place, the host's genetic propensity to produce T_H2 cytokines, pharmacologic factors, the costimulatory signals used during T-cell activation, the site of antigen entry, and the APC.

Role of cytokines

IL-4 promotes T_H2 cell development, whereas IL-12, produced by macrophages, dendritic cells, or eosinophils, induces T_H1 cells. It has been shown that the IL-12 receptor ([IL-12R] β_2) subunit, which is the binding and signal transducing component of the IL-12 receptor, is expressed on T_H1 but not T_H2 clones.⁵⁹ Interestingly, IL-4 inhibits the expression of IL-12R β_2 on T cells. In contrast, IL-12, IFN- α , and IFN- γ induces expression of the IL-12R β_2 chain, thereby providing a basis by which these cytokines induce differentiation of T_H1 cells. IL-18 activates the IFN- γ promoter at an activator protein-1 binding site and induces IFN- γ synthesis, thereby enhancing T_H1 cell development.⁶⁰ IL-4 has also been demonstrated to inhibit IFN- γ production and down-regulate the differentiation of T_H1 cells. Furthermore, mast cells and basophils also provide a source of T_H2 cytokines, which can be released on cross-linking of their high-affinity IgE receptor.⁶¹ The increased systemic and local skin expression of IL-4 by T cells and mast cells/basophils in AD would be expected to promote T_H2 cell development. It should be noted, however, that because T_H2 cells can still develop (albeit at a lower level) in IL-4 knockout mice there must be other factors contributing to T_H2 cell development as well.

Genetics

Although many genes are likely to be involved in the development of allergic diseases, there has been particular interest in the potential role of chromosome 5q31-33 because it contains a clustered family of cytokine genes (ie, IL-3, IL-4, IL-5, IL-13, and GM-CSF) that are expressed by T_H2 cells.⁶² Kawashima et al⁶³ examined linkage between markers at and near the IL-4 gene and

AD in 88 Japanese nuclear families. A case-control comparison suggested a genotypic association between the T allele of the -590C/T polymorphism of the IL4 gene promoter region with AD. Because the T allele is associated with increased IL4 gene promoter activity compared with the C allele, their data suggest that genetic differences in transcriptional activity of the IL4 gene influence AD predisposition. In addition, Hershey et al⁶⁴ reported an association of AD with a gain-of-function mutation in the α -subunit of the IL-4 receptor. The authors speculated that the R576 allele may predispose persons to allergic diseases by altering the signaling function of the receptor. Overall, these data support the concept that IL-4 gene expression plays a critical role in the expression of AD.

Pharmacologic factors

Mononuclear cells from patients with AD have increased cyclic AMP-phosphodiesterase (PDE) enzyme activity. This cellular abnormality contributes to the increased IgE synthesis by B cells and IL-4 production by T cells in AD because IgE and IL-4 production can be decreased in vitro by PDE inhibitors.⁶⁵ The elevated cyclic AMP PDE in atopic monocytes also contributes to the secretion of increased IL-10 and PGE₂. Both monocyte-derived IL-10 and PGE₂ inhibit IFN- γ production by T cells and may therefore contribute to the decreased IFN- γ production by cultured AD PBMCs. PDE inhibitors have also been found to reduce superantigen-induced IL-12-dependent expression of the CLA skin homing receptor on T cells from patients with AD.⁶⁶

Costimulatory signals

Complete activation of resting T cells require costimulatory signals independent of the engagement of T-cell receptors with the MHC plus peptide complex on APCs. In mice, it has been reported that the generation of T_H2 cells depends on the interaction of CD28 with B7.2.⁶⁷ To determine the potential role of B7.2 molecules in AD, we recently compared the expression of B7.1 versus B7.2 on B cells from patients with AD.⁶⁸ The expression of B7.2 on B cells of patients with AD was significantly higher than in healthy subjects or patients with psoriasis. In contrast, there was no significant difference in B7.1 expression among the 3 subject groups. Importantly, total serum IgE from AD patients and healthy subjects correlated significantly with B7.2 expression on B cells, suggesting a role for B7.2⁺ B cells in IgE synthesis. Anti-human B7.2, but not B7.1, mAb significantly decreased IgE production by PBMCs stimulated with IL-4 and anti-CD40 mAb. These data demonstrate the predominant expression of B7.2 in AD, but not psoriasis, and a novel role for this molecule in IgE synthesis. IL-4 and IL-13 have also been found to induce B7.2 expression on B cells, thereby providing an amplification loop for IgE synthesis in AD.⁶⁹

LCs in the lesional skin of AD predominantly express B7.2 compared with B7.1.⁷⁰ Furthermore, antibodies to B7.2 completely inhibited T-cell proliferation stimulated with *Dermatophagoides pteronyssinus* in the presence of

LCs. These data suggest that CD86 expression on LCs play an important role as costimulatory molecules for T-cell activation and may account for the increased T_H2 responses that occur after repeated antigen presentation by LCs.⁷¹

APCs

AD skin contain an increased number of IgE-bearing LCs, which appear to play an important role in cutaneous allergen presentation to T_H2 cells.⁷² In this regard, IgE-bearing LCs from AD skin lesions, but not LCs that lack surface IgE, are capable of presenting house dust mite allergen to T cells. These results suggest that cell-bound IgE on LCs facilitate capture and internalization of allergens into LCs before their processing and antigen presentation to T cells. IgE-bearing LC that have captured allergen likely activate memory T_H2 cells in atopic skin but may also migrate to the lymph nodes to stimulate naive T cells, there to further expand the pool of systemic T_H2 cells.

Binding of IgE to LCs occurs primarily through high-affinity IgE receptors. The importance of these IgE receptors on LCs is supported by the observation that the presence of Fc ϵ RI-expressing LCs bearing IgE molecules is required to provoke eczematous skin lesions by application of aeroallergens on the skin of atopic patients. In contrast to mast cells and basophils where the Fc ϵ RI is a tetrameric structure constitutively expressed at high levels, this receptor on LCs lacks the classic β -chain and its expression varies depending on the donor.⁷³ Healthy individuals and patients with respiratory allergy have low-level surface expression of Fc ϵ RI on their LCs, whereas Fc ϵ RI is expressed at high levels in the inflammatory environment of AD. High-level Fc ϵ RI expression not only enhances binding and uptake of allergens but the activation of LCs on receptor ligation.⁷⁴ Surface expression of Fc ϵ RI has been found to correlate with IgE serum levels. Furthermore, IL-4 strongly induces the cytoplasmic expression of the α -chain of Fc ϵ RI in dendritic cells and up-regulates the expression of the skin homing structures E-cadherin and CLA.⁷⁵ In contrast, IFN- γ inhibits Fc ϵ RI and E-cadherin expression.

Route of antigen entry

Although IgE-bearing LCs are likely to be involved in the presentation of allergen that enters AD skin through the epicutaneous route, their role in the presentation of antigen absorbed from the systemic circulation is still undetermined. In the case of ingested food allergens or aeroallergens that are inhaled and absorbed into the circulation from the respiratory mucosa, the APCs may be quite different than found with antigens absorbed from the surface of the skin. Of interest, the majority of macrophages and dendritic cells infiltrating into the dermis of AD skin lesions have IgE on their cell surface.³⁵ Circulating monocytes and dendritic cells have low-affinity and high-affinity IgE receptors.⁷⁶ These observations suggest that APCs loaded with allergens taken up in the respiratory or gastrointestinal tracts could circulate

and infiltrate into atopic skin to activate local T cells. In that scenario, allergens from the circulation may trigger degranulation of mast cells lining the dermal venules and the release of T_H2 cytokines, which would enhance T_H2 cell activation by allergens being presented by dermal macrophages and dendritic cells. Alternatively, because food and inhalant allergens have been found to expand peripheral blood skin-homing CLA^+ T cells, it is possible that local mucosal expansion of CLA^+ T cells can occur and that these T cells home to the skin.

IMMUNOLOGIC TRIGGERS

Food allergens

Numerous investigations have established that food allergy plays a pathogenic role in AD.^{77,78} On the basis of double-blinded, placebo-controlled food challenges (DBPCFC), approximately 40% of infants and young children with moderate to severe AD have food allergy. Although the dermatology literature has frequently not supported a role for foods in AD, a recent study by Eigenmann et al⁷⁹ demonstrated that 37% of unselected children with moderate to severe AD referred to a university dermatologist had food allergy. Guillet and Guillet⁸⁰ evaluated 250 children with AD and found the increased severity of AD and younger age of patients was directly correlated with the presence of food allergy. Removal of the food allergen from the patient's diet can lead to significant clinical improvement but requires a great deal of education because most of the common causal allergens (eg, egg, milk, wheat, soy, and peanut) contaminate many foods and are therefore difficult to avoid. Several studies also indicate that AD can be at least partially prevented by prophylactically eliminating the more highly allergenic foods (eg, eggs, milk, and peanut) from the diets of infants and breast-feeding mothers.^{81,82}

Laboratory studies supportive of a role for food allergy in AD include the observation that infants and young children with moderate to severe AD frequently have positive immediate skin tests or serum IgE directed to various foods. Positive food challenges are accompanied by significant increases in plasma histamine concentrations and eosinophil activation.^{77,83} Furthermore, children with AD who are chronically ingesting foods to which they are allergic have been found to have increased spontaneous basophil histamine release compared with children without food allergy. Immediate skin tests to specific allergens, however, do not always indicate clinical sensitivity and patients who outgrow AD frequently continue to have positive skin tests. May⁸⁴ first made a distinction between symptomatic versus asymptomatic hypersensitivity on the basis of the observation that AD patients with positive immediate food skin tests did not always have positive challenges to the foods implicated by IgE responses. These clinical observations suggest that the relationship between IgE and clinical AD is not exclusively dependent on IgE-mediated mast cell degranulation.

Importantly, IgE molecules can also participate in T cell-mediated reactions by binding to LCs by their high-affinity IgE receptors. Food allergen-specific T cells have been cloned from lesional skin and normal skin of patients with AD.^{85,86} In support of a role for food allergen-specific T cells in AD, patients with food-induced AD have been studied to analyze the relationship between tissue specificity of a clinical reaction to an allergen and the expression of skin-homing receptors on T cells activated in vitro by the relevant allergen.⁸⁷ In these studies the expression of CLA and L-selectin on T cells from children with casein-induced AD were assessed and compared for their CLA expression after stimulation in vitro with casein to T cells collected from patients with milk-induced gastroenteropathy or healthy control subjects. Casein-reactive T cells from patients with milk-induced eczema were found to have significantly higher levels of CLA than did *Candida albicans*-reactive T cells from the same patients and either casein- or *C albicans*-reactive T cells from nonatopic control subjects or noneczematous atopic patients. Overall, these studies provide strong scientific evidence that foods can play a role in the pathogenesis of AD in young children.

Aeroallergens

As atopic children grow older, inhalant allergens play a more important role in the pathogenesis of their AD.⁸⁸ Walker⁸⁹ first reported in 1918 that several of his patients had exacerbation of their AD on exposure to horse dander, timothy grass, or ragweed pollen. In the 1950s Tuft and Heck⁹⁰ reported that in patients with AD pruritus and eczematoid skin lesions developed after intranasal inhalation challenge with either *Alternaria* or ragweed pollen but not placebo challenges. More recently, a DBPCFC study demonstrated that inhalation of house dust mites by bronchial challenge resulted both in new AD lesions and exacerbation of existing skin lesions.⁹¹

Most reports, however, have focused on the epicutaneous application of aeroallergens by patch test techniques. In these studies patch testing of uninvolved atopic skin with aeroallergens gave rise to eczematoid reactions in 30% to 50% of patients with AD.^{92,93} Positive reactions were observed to various allergens including dust mite, weeds, animal danders, and molds. In contrast, patients with respiratory allergy and healthy volunteers rarely have positive allergen patch tests. Although it is established that patch tests with allergens can give rise to eczematoid reactions, there is considerable variation in the performance and interpretation of these tests. The allergens used in this testing has not been standardized; whether to apply allergens to intact or mildly abraded skin has not been established and grading of positive responses varies according to medical center. Therefore the clinical usefulness of this test is still questionable although it continues to be used as a research tool.

Several studies have examined whether avoidance of aeroallergens results in clinical improvement of AD. Most of these reports have involved uncontrolled trials in which patients were placed in mite-free environments

(eg, hospital rooms) through the use of acaricides or impermeable mattresses covers. Such methods have invariably led to improvement in AD. One double-blind placebo-controlled study that used a combination of effective mite-reduction measures in the home has been reported.⁹⁴ Although both active and control groups decreased Der p 1 concentrations in carpeting, the reduction in the amount of dust was greater on the mattresses in the active group, and the disease improved significantly more in the active treatment group.

These clinical studies suggest that inhalation or contact with aeroallergen may exacerbate AD. Laboratory data supporting a role for inhalants include the finding of IgE antibody to specific inhalant allergens in most patients with AD. Indeed, a recent study found that 95% of sera from AD patients had IgE to house dust mites compared with 42% of asthmatic subjects.⁹⁵ The degree of sensitization to aeroallergens is directly associated with the severity of AD.⁹⁶ The isolation from AD skin lesions and allergen patch test sites of T cells that recognize *D pteronyssinus* (Der p 1) and other aeroallergens provides further evidence that the inflammatory response in AD can be elicited by inhalant allergens.^{86,97}

Microbes

Patients with AD have an increased tendency for the development of bacterial and fungal skin infections. *S aureus* is found in more than 90% of AD skin lesions. In contrast, only 5% of healthy subjects harbor this organism. The density of *S aureus* on inflamed AD lesions without clinical superinfection can reach up to 10⁷ colony-forming units per square centimeter on lesional skin. The importance of *S aureus* is supported by the observation that even AD patients without superinfection show a reduction in severity of skin disease when treated with a combination of antistaphylococcal antibiotics and topical corticosteroids.⁹⁸

Recent studies suggest that one strategy by which *S aureus* exacerbates or maintains skin inflammation in AD is by secreting a group of toxins known to act as superantigens that stimulate marked activation of T cells and macrophages. Several lines of investigations support a role for superantigens in AD (Fig 2). First, more than half of AD patients have *S aureus* cultured from their skin and the bacteria secrete superantigens such as enterotoxins A and B and TSST-1.^{53,99,100} An analysis of the skin-homing CLA⁺ T cells from these patients as well as their skin lesions reveals that they have undergone a T-cell receptor (TCR) V β expansion consistent with superantigenic stimulation.^{101,102} Second, most AD patients make specific IgE antibodies directed against the staphylococcal toxins found on their skin.^{53,99,100} Basophils from patients with antitoxin IgE release histamine on exposure to the relevant toxin but not in response to toxins to which they had no specific IgE.⁵³ Third, a correlation has been found between the presence of IgE antisuperantigens and the severity of AD.^{99,100} These patients had increased IgE levels to specific allergens. By use of a humanized murine model of skin

inflammation, *S aureus* superantigen plus allergen was shown to have an additive effect in inducing cutaneous inflammation.¹⁰³ Superantigens also augment allergen-specific IgE synthesis and induce corticosteroid resistance, suggesting that several mechanisms exist by which superantigens could aggravate the severity of AD.^{104,105} Fourth, the superantigen staphylococcal enterotoxin (SE) B applied to the skin can induce skin changes of erythema and induration, and the infiltrating T cells are selectively expanded in response to SEB.^{106,107} Furthermore, in a prospective study of patients recovering from toxic shock syndrome, it was found that 14 of 68 patients had chronic eczematoid dermatitis, whereas no patients recovering from gram-negative sepsis had eczema.¹⁰⁸ These investigators concluded that superantigens may induce an atopic process in the skin. It is therefore of interest that superantigens have been demonstrated to induce T-cell expression of the skin-homing receptor by stimulation of IL-12 production.¹⁰⁹ In the case of AD, we have proposed that staphylococcal superantigens secreted at the skin surface could penetrate inflamed skin and stimulate epidermal macrophages or LCs to produce IL-1, TNF, and IL-12. Local production of IL-1 and TNF induces the expression of E-selectin on vascular endothelium,¹¹⁰ allowing an initial influx of CLA⁺ memory/effector cells. Local secretion of IL-12 could increase CLA expression on those T cells activated by allergen or superantigen and thereby increase their efficiency of T-cell recirculation to the skin, perhaps including areas with only low levels of vascular E-selectin and minimal inflammatory activity. IL-12 secreted by toxin-stimulated LCs that migrate to skin-associated lymph nodes (and serve as APCs therein) could up-regulate the expression of CLA and influence the functional profile of virgin T cells activated by the toxins, thereby creating additional skin-homing memory-effector T cells. Together, these mechanisms would amplify the initial cutaneous inflammation in AD, creating conditions favoring staphylococcal skin colonization.

There has also been considerable interest in fungal infections, particularly in *Malassezia furfur* (*Pityrosporum ovale* or *Pityrosporum orbiculare*) as a pathogen in AD. *M furfur* is a lipophilic yeast commonly present in the seborrheic areas of the skin. IgE antibodies against *M furfur* is commonly found in AD patients and most frequently in patients with head and neck dermatitis.¹¹¹ In contrast, IgE sensitization to *M furfur* is rarely observed in healthy control subjects or asthmatic patients. Positive allergen patch test reactions to this yeast have also been demonstrated. The potential importance of *M furfur* as well as other dermatophyte infections is further supported by the reduction of AD skin severity in such patients after treatment with antifungal agents.^{112,113}

Autoallergens

Since the 1920s several investigators have demonstrated that human skin dander could trigger immediate hypersensitivity reactions in the skin of patients with severe AD, suggesting that they made IgE against

autoantigens in the skin.^{114,115} In 1963 Hashem et al¹¹⁶ reported that human skin extracts could induce proliferation in PBMCs from patients with AD. Interest in autoallergy as a trigger for AD has laid dormant until recently when Valenta et al¹¹⁷ reported that the majority of sera from patients with severe AD contain IgE antibodies directed against human proteins. One of these IgE-reactive autoantigens has recently been cloned from a human epithelial complementary DNA expression library and designated Hom s 1, which is a 55-kd cytoplasmic protein in skin keratinocytes.¹¹⁸ Such antibodies were not detected in patients with chronic urticaria, systemic lupus erythematosus, or graft-versus-host disease or in healthy control subjects. Although the autoallergens characterized to date have mainly been intracellular proteins, they have been detected in IgE immune complexes of AD sera, suggesting that release of these autoallergens from damaged tissues could trigger IgE- or T cell-mediated responses. These data suggest that, although IgE immune responses are initiated by environmental allergens, allergic inflammation can be maintained by human endogenous antigens, particularly in severe AD.

AD AS A MODEL OF ATOPIC DISEASE PROGRESSION

Fig 1 depicts key elements of the pathogenesis and progression of AD. First, the setting of this illness takes place in hosts who are highly allergic with a genetic tendency toward overexpression of T_H2 cytokines. This is reflected in a systemic T_H2 response with high serum IgE levels, eosinophilia, and an expansion of T cells expressing IL-4, IL-5, and IL-13 in individuals with an increased tendency for the development of respiratory allergy.

Second, once the process of skin inflammation is elicited, there is a clear-cut evolution from uninvolved skin, which has a sparse infiltrate of T_H2 cells, to acute papulovesicular eruptions with epidermal spongiotic changes and a marked influx of T_H2 cells. The activation of T_H2 cells by epicutaneous application of allergens is likely to involve allergen capture and presentation by IgE-bearing LCs. However, ingestion of foods or inhalation of aeroallergens may also involve mucosal APCs, which become armed with allergens and activate T cells, which then home to the skin and respond to locally expressed chemokines such as CTACK/CCL27. Alternatively, mucosal APCs could migrate to directly activate T cells in the skin. T_H2 cytokine release from T cells and mast cells also enhances development of T_H2 cells and induces the release of C-C chemokines such as eotaxin from various cell types, including keratinocytes, fibroblasts, and endothelial cells. Prolonged skin inflammation results in chronic AD associated with epidermal hyperkeratosis, dermal fibrosis, and lichenification. Unlike acute AD, the chronic inflammatory response is dominated by a T_H1 response driven by the subsequent infiltration of IL-12 expressing eosinophils, dendritic cells, and macrophages that follows the initial T_H2 response. The mechanism for increased IL-12 expression during

chronic AD is not known but may be related to the ability of IL-4 to induce IL-12 expression by eosinophils.¹¹⁹ In the case of dendritic cells and macrophages, microbial superantigens are known to be a potent inducer of IL-12 production.¹²⁰ IFN- γ , but not IL-4, has been correlated with the clinical severity of AD.⁴² This may be related to the capacity of IFN- γ to enhance eosinophil viability, augment eosinophil activation and cytotoxic activity, activate vascular endothelial molecules, which increase the infiltration of eosinophils, thereby contributing to chronic AD.^{121,122}

Third, atopic skin inflammation not only involves allergen-specific responses but non-antigen-specific mechanisms that amplify inflammatory responses. This is reflected in studies demonstrating that AD is associated with a lower itch threshold, cutaneous hyperreactivity, and an overly active inflammatory response. It is known that scratching plays a key role in the elicitation of eczematoid skin lesions. Once the itch-scratch cycle is triggered, mechanical trauma to the keratinocytes results in the release of a proinflammatory cytokine cascade that contributes to the infiltration of cells into the skin.

Finally, a number of studies indicate that AD is associated with defective skin barrier function. Although these changes may be related to the constant scratching and immune activation that is continuing, there are also reports that these patients have decreased ceramide levels in their skin, which may lead to reduced water binding capacity, higher transepidermal water loss, and decreased water content.¹²³ These changes also contribute to increased antigen absorption into the skin and therefore create a vicious cycle leading to further immune activation and perpetuation of skin inflammation.

MANAGEMENT OF AD

First-line therapy

Given the complexity of the inflammatory cascades that lead to AD, a multipronged approach is required for successful treatment (Table II). This includes the use of skin hydration, topical corticosteroids, and identification and elimination of exacerbating factors including irritants, allergens, emotional stressors, and infectious agents.¹²⁴ The maintenance of daily skin care, in particular bathing to hydrate the skin followed by application of an effective moisturizer and the appropriate use of topical corticosteroids to reduce skin inflammation, is critical for control of pruritus.

Although it is well established that patients with moderate to severe persistent asthma should be maintained on inhaled corticosteroid therapy, maintenance topical corticosteroids in AD is generally avoided because of concerns about potential side effects, particularly local skin atrophy. However, it is well established that even uninvolved skin of AD patients has an inflammatory cell infiltrate and manifests cutaneous hyperreactivity.^{15,34} To address the potential role of intermittent treatment with topical corticosteroids as part of maintenance therapy in adult patients with recurring AD, Van Der Meer et al¹²⁵

carried out a 2-phase multicenter study. In phase 1, patients with moderate to severe AD were treated for 2 weeks with topical fluticasone propionate (FP). Patients whose AD had completely healed were entered into phase 2, which consisted of topical FP versus placebo ointment applied to healed skin lesions 2 times per week for 16 weeks. Patients treated with intermittent FP were significantly more successful in maintaining the skin improvements achieved after the initial treatment phase with a significantly reduced risk of relapse. Future studies are needed to confirm the role of intermittent dosing of topical corticosteroid as maintenance therapy for patients with frequently recurring AD. Major issues will include its safety in pediatric patients and the length of such maintenance therapy.

In selected patients, first-generation oral H₁ antihistamines may offer some symptomatic relief of their pruritus. However, they are generally helpful, mainly for sedation and urticaria, which can be found in a subset of patients with AD. Some of the newer nonsedating antihistamines (eg, cetirizine) may also have anti-inflammatory properties, and they have been found to have a high safety profile in the treatment of children with AD.¹²⁶ A written treatment plan should be provided to all patients. Patient education is essential to encourage compliance with treatment plans. For additional information the patient can contact the National Eczema Association for Science and Education (800/818-7456; <http://eczema-assn.org>).

For patients who are difficult to manage, a number of factors must be considered. These include the possibility that the incorrect diagnosis has been made. In any patient who is more than 21 years old the possibility of cutaneous T-cell lymphoma or allergic contact dermatitis must be ruled out. Immunodeficiency disorders should be considered in infants with recurrent infections or atypical rashes. Lack of adherence to therapy is a major cause of treatment failure. Hospitalization should be considered in any patient who is erythrodermic or who has severe AD resistant to therapy. In many cases removing the patient from environmental triggers (eg, food allergens, aeroallergens, or microbial infection) and emotional stressors, combined with intense patient education and assurance of compliance with topical skin care results in significant improvement of AD. Clearing of the skin allows the patient to undergo appropriate skin testing and controlled challenges to identify allergenic triggers.

For patients who are resistant to conventional therapy, adjunctive therapies should be considered. Use of tar preparations can reduce the need for topical corticosteroids. UV light therapy may be useful in the treatment of chronic recalcitrant AD because it has anti-inflammatory, antibacterial, and immunomodulatory effects. UVA has been found to be more beneficial than UVB alone. However, the combination of UVA and UVB is better than either therapy alone. Photochemotherapy with oral psoralen therapy followed by UVA may also be helpful in severe AD. It should be reserved for patients with more recalcitrant skin disease because of the expense and the potential increased risk of skin cancer.

TABLE II. Emerging concepts in the management of atopic dermatitis

Importance of skin barrier dysfunction
Complexity of chronic inflammatory response
Importance of early intervention
Allergens and superantigens alter response to steroids
Intermittent use of topical steroids to prevent relapses
New role for topical macrolide immunosuppressants

Alternative therapies

Interferons. Several studies, including a multicenter, double-blinded, placebo-controlled trial, have demonstrated that recombinant IFN- γ is effective and safe in the treatment of moderate to severe AD.¹²⁷ Clinical improvement on IFN- γ therapy correlates with decreased total circulating eosinophil counts.¹²⁸ Thus IFN- γ may act on the systemic allergic response to reduce local infiltration of eosinophils. Recombinant IFN- α has also been used to treat patients with AD in several small uncontrolled trials. A few reports suggest some clinical benefit with this, but other studies have not confirmed this finding, although a significant decrease in circulating eosinophils has been noted.¹²⁹ Unfortunately, the high cost and benefit for only a subset of patients have prevented the further development of interferons for AD.

Allergen immunotherapy. Unlike for allergic rhinitis and extrinsic asthma, immunotherapy with aeroallergens has not been proved to be efficacious in the treatment of AD. There are anecdotal reports of exacerbation of disease activity and other reports that suggest improvement. Most studies have been flawed by lack of adequate blinding, small numbers of patients studied, high drop-out of subjects, dramatic placebo effects, etc. As with asthma, AD has many nonallergic triggers; therefore patients have to be carefully selected for immunotherapy in that it must be clearly demonstrated the putative allergen has a role in the pathogenesis of AD. Well-controlled studies are therefore still required to determine the role for immunotherapy with this disease.

Intravenous Ig. Intravenous γ -globulin (IVIG) has been demonstrated to have immunomodulatory and anti-inflammatory actions. An open-labeled study of 8 patients with steroid-dependent asthma reported that IVIG, given at 2 g/kg, resulted in clinical improvement, steroid reduction, and a reduction in skin test reactivity to allergens.¹³⁰ In a separate group of steroid-dependent asthmatic subjects, Spahn et al¹³¹ found that treatment with IVIG also improved glucocorticoid receptor binding affinity and had a synergistic anti-inflammatory effect with corticosteroids. Because chronic inflammation and T-cell activation appear to play a critical role in the pathogenesis of asthma and AD, there may also be a rationale for considering IVIG in the treatment of severe AD because it has been found to reduce IL-4 protein expression in AD.¹³² Although of interest, these observations are anecdotal and require confirmation in larger numbers of patients with better controlled study designs.

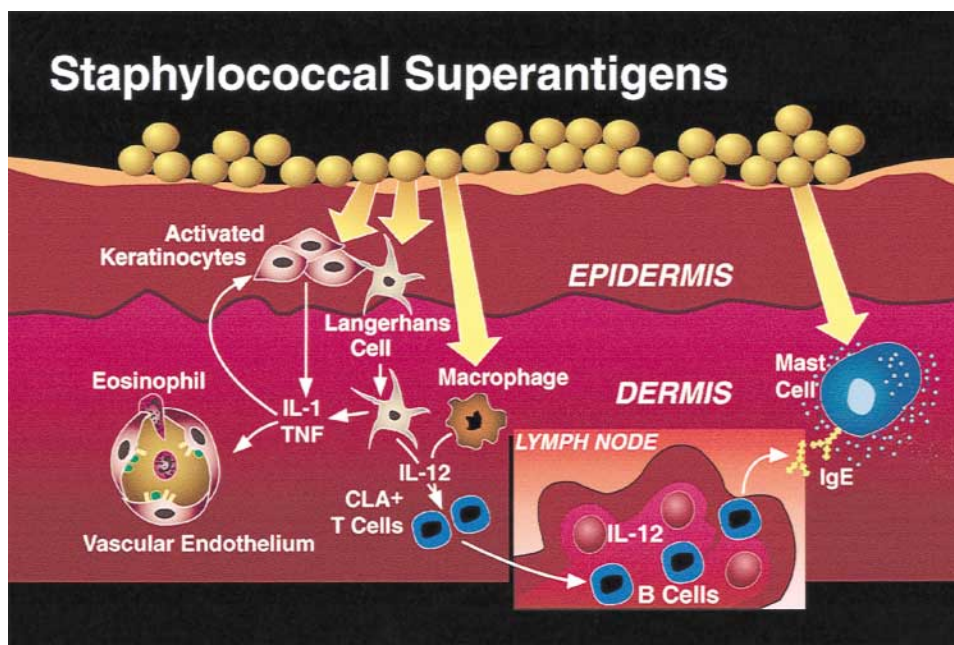


FIG 2. Immune mechanisms of staphylococcal superantigen action.

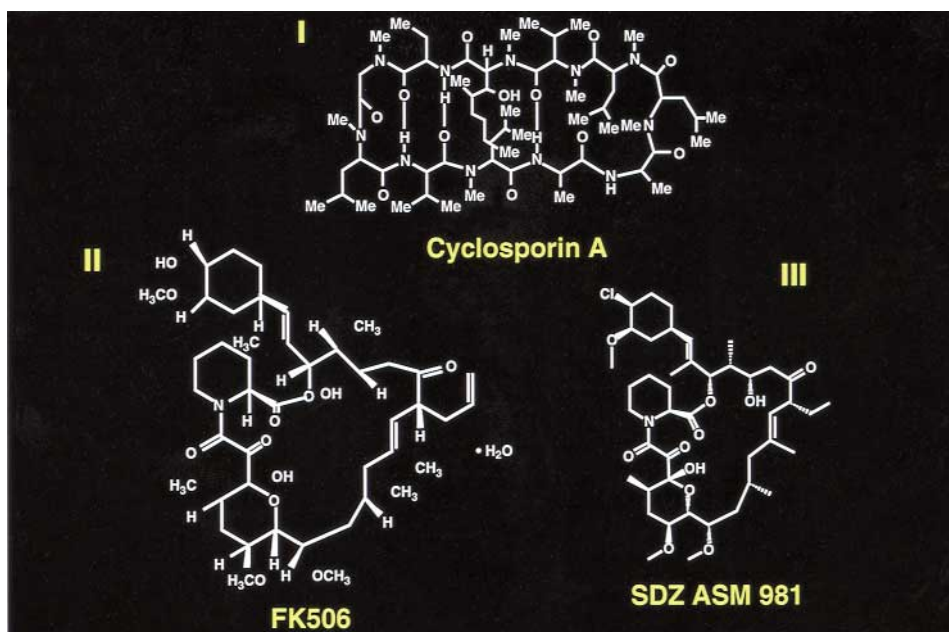


FIG 3. Structures of immunosuppressive macrolides.

Leukotriene antagonists. Because leukotriene antagonists are effective in the treatment of asthma and eosinophils are thought to play a key role in the pathogenesis of AD, zafirlukast was used in the treatment of 4 patients with poorly controlled AD.¹³³ All 4 patients had a significant reduction in the clinical severity of their AD. More extensive and controlled studies are needed to determine the role of leukotriene antagonists in the treatment of AD.

Chinese herbal medicine. Chinese herbs have been

reported to be useful in severe cases of AD. However, initial enthusiasm for this form of therapy has been blunted by reports of liver toxicity.¹³⁴ Furthermore, the content of Chinese herbal medicine is poorly characterized. Indeed, a survey of 10 formulations of Chinese herbal therapies found that 7 of them contained significant levels of corticosteroids.¹³⁵ Most recently, a controlled trial of traditional Chinese herbal medicine failed to find a benefit in the treatment of recalcitrant AD.¹³⁶

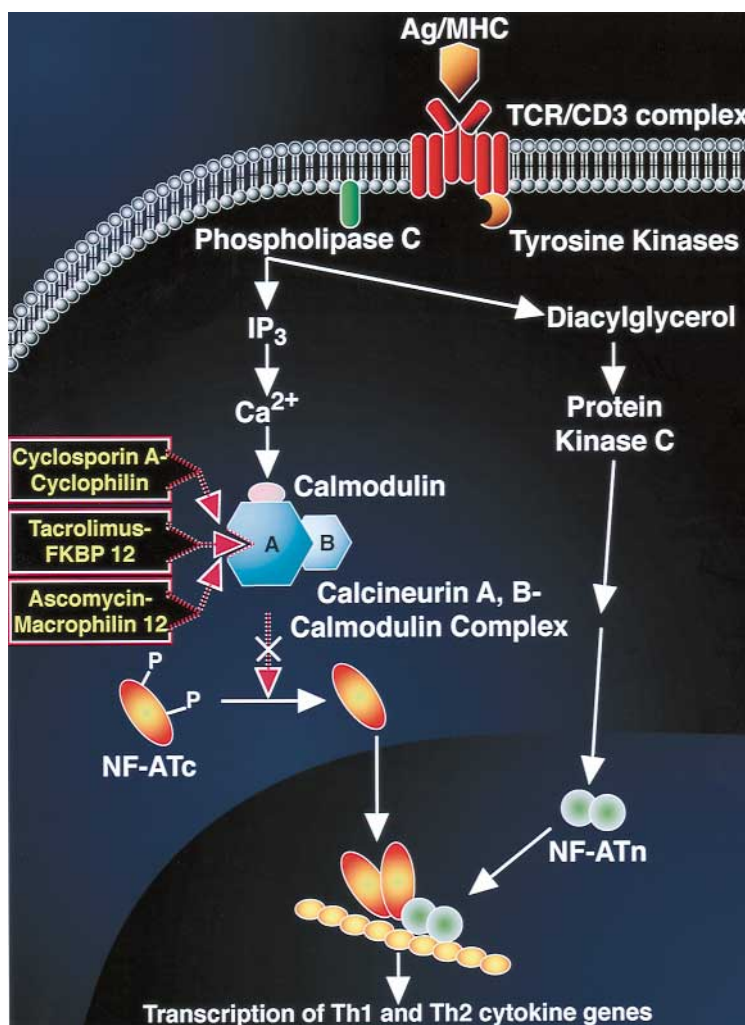


FIG 4. Mechanism of immunosuppressive macrolide action in T cells. Antigen-mediated stimulation of the T cell receptor (TCR) leads to phospholipase C-mediated generation of diacylglycerol and inositol triphosphate (IP_3), activation of protein kinase C, an increase in cytosolic calcium, formation of an activated calmodulin-cal-cineurin complex, and formation of nuclear factor of activated T cells (NF-ATc) required for transcription of the IL-2 gene. Cyclosporin A, tacrolimus, and ascomycins bind to their respective immunophilins to inhibit the phosphatase action of calcineurin and block nuclear translocation of the cytoplasmic subunit of the nuclear factor of activated T cells transcription factor.

Phosphodiesterase inhibitors. Leukocytes from patients with AD have been shown to have increased cyclic AMP-PDE enzyme activity. This abnormality is most pronounced in atopic monocytes, which have been shown to have a unique, highly active PDE isoenzyme. Monocytes from patients with AD have been demonstrated to produce elevated levels of PGE_2 and IL-10, which both inhibit IFN- γ production. PDE inhibitors such as Ro 20-1724 have been found to reduce IL-10 and PGE_2 by atopic monocytes. Preliminary clinical studies of topical application of high-potency PDE inhibitors have demonstrated them to be of clinical benefit in AD.⁶⁵

Macrolide immunosuppressants. Cyclosporin A is a potent immunosuppressive drug that acts primarily on T cells by suppressing cytokine transcription (Fig 3). The drug binds to an intracellular protein, cyclophilin, and

this complex in turn inhibits calcineurin, a molecule required for initiation of cytokine gene transcription (Fig 4). Several short-term studies have demonstrated that patients with severe AD refractory to treatment with topical corticosteroids can benefit from treatment with oral cyclosporin (5 mg/kg/d). Treatment with cyclosporine was associated with reduced skin disease and improved quality of life.¹³ However, side effects (nausea, abdominal discomfort, paresthesias, hypertension, hyperbilirubinemia, and renal impairment) dictate caution in the use of this drug. Furthermore, discontinuation of treatment frequently results in rapid relapse of skin disease. Because of concerns over systemic side effects from oral cyclosporine, the efficacy of topically administered cyclosporine has been studied in AD. However, this approach has not been efficacious.

Tacrolimus or FK506, a macrolide lactone isolated from *Streptomyces tsukbaensis*, is a potent immunosuppressive agent with a spectrum of activity similar to that of cyclosporin.¹³⁷ Its smaller molecular size and higher potency compared with cyclosporine suggested that it could be effective as a topical agent (Fig 3). Although it is structurally unrelated to cyclosporin A, tacrolimus also interacts with a cyclophilin-like cytoplasmic protein, FK506 binding protein, and this complex in turn inhibits calcineurin, interfering with gene transcription of multiple cytokines including IL-2 (Fig 4).¹³⁸ Several uncontrolled studies and 2 multicenter controlled studies suggest that FK506 in ointment form (tacrolimus) can effectively reduce the clinical symptoms of AD with markedly diminished pruritus within 3 days of initiating therapy, with no evidence of systemic side effects.^{139,140}

The mechanism by which tacrolimus exerts its beneficial effects remains to be elucidated, although it likely involves the inhibition of IL-2, IL-4, and IL-5 gene transcription. Of note, skin biopsy results after 3 and 7 days of treatment with topical tacrolimus has revealed markedly diminished T-cell and eosinophilic infiltrates. Tacrolimus also inhibits the transcription and release of other T cell-derived cytokines such as IL-3, IFN- γ , TNF- α , and GM-CSF, which can also contribute to allergic inflammation. Of note, other cell types important in allergic skin inflammation including mast cells, basophils, eosinophils, keratinocytes, and LCs have tacrolimus (FK506)-binding proteins and down-regulate their mediator or cytokine expression after treatment with tacrolimus. Importantly, these anti-inflammatory effects occur without inducing skin atrophy.¹⁴¹

SDZ ASM 981, an immunosuppressant that acts like FK506, also has been shown to inhibit T_H1 and T_H2 cytokines (Fig 3).¹⁴² A randomized, double-blind, placebo-controlled study has shown that topical application of 1% SDZ ASM 981 cream twice daily significantly improved the clinical symptoms, including pruritus and excoriations, of patients with AD.¹⁴³ No significant adverse effects were noted in the study. Because recent studies suggest that the T-cell activation in AD is biphasic with activation of the T_H2 cytokines during the acute phase and increased expression of the T_H1 cytokines in chronic lesions, the capacity of tacrolimus and SDZ ASM 981 to inhibit the activation of multiple cell types and different cytokines may account for their ability to effectively reduce skin inflammation in AD.

FUTURE DIRECTIONS

Corticosteroids, UV therapy, and the immunosuppressant macrolides are all therapeutic agents that are likely to be effective in controlling the complex inflammatory cascades of chronic AD. However, future studies are needed to focus on strategies preventing the initial development of AD. Given the central role of T_H2 cytokines and chemokines in the development of allergic skin inflammation, strategies directed at reducing T_H2 responses and blocking the action of chemokines by

antagonists of CCR3 and CCR4 will be important. Further studies are also needed to examine the potential role of IFN- γ , IL-12, and IL-18 in restoring the shift toward a more balanced T_H0 response with equal production of T_H1 and T_H2 cytokines. There is also a strong rationale for examining the effect of therapeutic agents capable of blocking the actions of IL-4 and IL-5. Anti-IL-5 antibody has been shown to block eosinophil infiltration in sensitized animals whether administered before or after allergen challenge.¹⁴⁴ Preliminary data with a humanized mAb against IL-5 in a monkey model of asthma suggests that a single dose can inhibit eosinophil accumulation for up to 3 months.¹⁴⁵ To date, anti-IL-5 therapy has not been examined in vivo in patients with AD, but these encouraging studies in respiratory allergy suggest that such an approach should also be considered in AD.

Similarly, it has been found in animal models that T_H2 cells mediate skin inflammation with use of IL-4-dependent mechanisms.¹⁹ Thus it would be of interest to determine the clinical effects of blocking the action of IL-4 in patients with AD. Indeed, in vitro studies have demonstrated that soluble IL-4 receptor molecules bind IL-4, resulting in suppression of IL-4-mediated T- and B-cell functions.¹⁴⁶ Preliminary clinical trials in patients with asthma with soluble IL-4 receptors have found it to be safe and effective in treating moderate asthma.¹⁴⁷

The recent development of humanized anti-IgE antibodies¹⁴⁸ that are nonanaphylactogenic also offers the hope that it may be possible to eliminate or reduce IgE responses, although it will be more difficult to neutralize IgE in AD because of the high serum IgE levels in these patients. Of note, elimination of the IgE response may have less importance in patients with continuing T_H2-mediated allergic inflammatory responses. Indeed, in animal models of AD allergic inflammation of the skin was elicited to the same extent in wild-type and IgE knockout mice.⁴⁴ Thus the combination of several approaches will be needed to effectively interrupt the complex inflammatory cascades associated with allergic diseases.

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